

U.S. Application No. 09/806,989
Amendment dated October 25, 2005

Confirmation No. 7861

Amendments to the Specification:

Please replace the paragraph beginning at page 4, line 23 with the following amended paragraph:

The consequence of lack of HISS release is the absence of HISS results in severe insulin resistance. In this situation, the pancreas is required to secrete substantially larger amounts of insulin in order that the glucose in the blood is disposed of to prevent hyperglycemia from occurring. If this condition persists, insulin resistance will progress to a state of type 2 diabetes (non-insulin dependent diabetes mellitus) and eventually will lead to a complete exhaustion of the pancreas thus requiring the patient to resort to injections of insulin. Thus, any condition in which the hepatic parasympathetic reflex is dysfunctional will result in insulin resistance.

Please replace the paragraph beginning at page 8, line 11 with the following amended paragraph:

The compounds of the present invention can be considered, generally, as members of the groups of nitric oxide agonists and NO donors. Examples of such compounds include, but are not limited to: 3-morpholinosydnonimine (SIN-1), sodium nitrite, nitroprusside, S-nitroso-N-acetyl-D, L-penicillamine (SNAP).

Please replace the paragraph beginning at page 9, line 17 with the following amended paragraph:

To quantify insulin sensitivity in rats a modified euglycemic clamp method for conducting a rapid insulin sensitivity test (RIST) (29) was used. Interruption of the hepatic reflex response to insulin by surgical denervation of the liver or atropine results instant and reversible (26-28) insulin resistance in skeletal muscles (27). To evaluate the involvement of NO, two nitric oxide synthase (NOS) antagonists were used, N-nitro-L-arginine methyl ester (L-NAME) and N-monomethyl-L-arginine (L-NMMA). The insulin resistance produced by intravenous versus intraportal NOS antagonism was also compared to determine if the liver was the site of NO action. 3-morpholinosydnonimine (SIN-1), a NO donor, was administered intravenously or intraportally to reverse the insulin resistance produced by L-NMMA.

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Please replace the paragraph beginning at page 23, line 19 with the following amended paragraph:

Previous studies (27-29) are consistent with the statement that animals respond to insulin by activation of a hepatic parasympathetic reflex release of a hepatic insulin sensitizing substance (HISS) that sensitizes skeletal muscle to the effects of insulin. Surgical or pharmacological ablation of the hepatic parasympathetic nerves leads to insulin resistance. Intraportal, but not intravenous, acetylcholine is capable of reversing the insulin resistance caused by denervation. The hepatic parasympathetic reflex control of insulin action is mediated through hepatic NO and hepatic NOS antagonism and hepatic denervation produce insulin resistance that is reversible by providing NO to the liver using a NO donor. The parasympathetic reflex release of HISS is concluded to be NO-mediated.

Please replace the paragraph beginning at page 24, line 15 with the following amended paragraph:

It had been shown that L-NAME is both a nitric oxide synthase (NOS) inhibitor and a muscarinic receptor antagonist (2). Although the mechanism or location of action was not described, it was previously determined that L-NAME produces insulin resistance that does not act through muscarinic antagonism (22), thus indicating that both L-NAME and L-NMMA are suitable tools for the present purpose.